

REMARKS

Status of the Claims

Claims 1, 4, 7-12 and 19-21 are currently pending in the application. Claims 1-12, 19 and 20 stand rejected. The Examiner objects to claims 7 and 8. Claims 1, 4, 11, 12 and 19 have been amended as set forth herein. Claims 2, 3, 5 and 6 have been cancelled herein. All amendments and cancellations are made without prejudice or disclaimer. New claim 21 has been added herein. No new matter has been added by way of the present amendments. Specifically, the amendment to claims 1 and 4 are supported by original claims 2, 3, 5 and 6. Amendments to claims 11 and 12 are made only to update dependency of these claims.

Amendments to claim 19 are supported by the specification at, for instance, page 14. New claim 21 is supported by the specification at, for instance, page 14, lines 2-4. Reconsideration is respectfully requested.

Objections to the Claims

The Examiner objects to claims 7 and 8 for containing non-elected subject matter. (*See*, Office Action of May 5, 2006, at page 6, hereinafter, "Office Action"). Claims 7 and 8 were previously indicated as being allowed in the Office Action of September 22, 2005 and the Advisory Action of January 27, 2006. The Examiner states that part g) of claim 7 was elected in the response to the Restriction Requirement filed on October 7, 2004. Thus, the Examiner is apparently requesting Applicants to cancel the non-elected subject matter. However, part g) of claim 7 was elected in response to an **election of species**. It appears that the elected species is

allowable and therefore, according to M.P.E.P. § 809.02(a), the Examiner is now required to also examine a reasonable number of similar non-elected species.

Reconsideration and withdrawal of the objection to claims 7 and 8 are therefore respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 19 stands rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. (*See*, Office Action, at page 6). Applicants traverse the rejection as set forth herein.

The Examiner states that claim 19 is missing critical components of the trap vector, such as the SA, IRES and marker gene. (*Id.* at pages 6-7).

Although Applicants do not agree that claim 19 lacks enablement as originally presented, to expedite prosecution, claim 19 has been amended, without prejudice or disclaimer, to recite, in part, “wherein both trap vectors (a) and (b) further comprise at least one splice acceptor site and at least one internal ribosomal entry site,” as suggested by the Examiner. The amendment to claim 19 is supported throughout the specification at, for instance, page 14. Furthermore, claim 19 already recites, in part, “a marker gene.” Thus, claim 19, at least as amended, recites all critical components of the trap vector and is fully enabled by the specification.

Reconsideration and withdrawal of the enablement rejection of claim 19 is respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Elledge et al., U.S. Patent No. 5,851,808

Claims 1 and 4 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Elledge et al., U.S. Patent No. 5,851,808 (hereinafter referred to as “Elledge et al.”). (*See*, Office Action, at page 3). Applicants traverse the rejections as set forth herein.

The Examiner states that Elledge et al. disclose a vector comprising a wild type *loxP* and a mutant *loxP*, wherein the mutant *loxP* has a mutation either in the first inverted repeat sequence or the second inverted repeat sequence. (*Id.*).

Although Applicants do not agree that the disclosure of Elledge et al. anticipates the presently claimed invention, as recited in claim 1, to expedite prosecution, claim 1 has been amended herein, without prejudice or disclaimer, to recite the limitations of claims 2 and 3. Claims 2 and 3 have been cancelled herein without prejudice or disclaimer. Since claims 2 and 3 are not rejected as being anticipated by Elledge et al., claim 1, at least as amended, is not anticipated by Elledge et al. because Elledge et al. do not disclose each and every limitation of amended claim 1. “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” (*See, Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)).

Furthermore, although Applicants do not agree that the disclosure of Elledge et al. anticipates the presently claimed invention, as recited in claim 4, to expedite prosecution, claim 4 has been amended herein, without prejudice or disclaimer, to recite the limitations of claims 5

and 6. Claims 5 and 6 have been cancelled herein without prejudice or disclaimer. Since claims 5 and 6 are not rejected as being anticipated by Elledge et al., claim 4, at least as amended, is also not anticipated by Elledge et al. because Elledge et al. do not disclose each and every limitation of amended claim 4.

Reconsideration and withdrawal of the anticipation rejection of claims 1 and 4 are respectfully requested.

Albert et al., *Plant J.*, 7(4):649-659, 1995

Claims 9 and 10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Albert et al., *Plant J.*, 7(4):649-659, 1995 (hereinafter “Albert et al.”). (*Id.* at page 3). Applicants traverse the rejection as set forth herein.

The Examiner states that Albert et al. disclose a vector comprising two loxP sites (wild-type and mutant) that have a low in recombination efficiency (cannot be recombined) and that the mutation is in the inverted repeat region of the *loxP* site, not the spacer region.

However, Applicants bring the following important distinguishing feature of the Albert et al. vector to the Examiner’s attention: the vector disclosed in Albert et al. has two loxP sites that are oriented in opposite direction to each other. In contrast, the vector according to claims 9 and 10 has two *loxP* sites that are always oriented in the same direction. According to claims 9 and 10, no vector is generated in which the two *loxP* sites are oriented in the opposite directions, as in Albert et al.

Therefore, Albert et al. do not disclose each and every limitation as presently recited by claims 9 and 10, and as required to establish anticipation. “A claim is anticipated only if each

and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” (See, *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)).

Reconsideration and withdrawal of the anticipation rejection of claims 9 and 10 are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Elledge et al. & Albert et al.

Claims 2, 3, 5 and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Elledge et al. in view of Albert et al. (See, Office Action, at page 4). Claims 2, 3, 5 and 6 have been cancelled herein without prejudice or disclaimer, thus obviating the obviousness rejection of these claims.

Leboulch et al., U.S. Patent No. 5,928,914, Araki et al. and Albert et al.

Claims 11, 12, 19 and 20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Leboulch et al., U.S. Patent No. 5,928,914 (hereinafter, “Leboulch et al.”) in view of Araki et al., *Targeted Integration of DNA Using Mutant Lox Sites in Embryonic Stem Cells*, *Nuc. Acids Res.*, 1997, 25(4):868-872 (hereinafter, “Araki et al.”) and Albert et al. (See, Office Action, at page 5). Applicants traverse the rejection as hereinafter set forth.

The Examiner admits that Leboulch et al. do not disclose use of loxP in the same vector as lox71 or lox66. However, the Examiner relies on the additional disclosure of Araki et al. for

these missing limitations. The Examiner further states that it would have been obvious to substitute lox66 and lox71 for loxP2 and loxP3.

The Examiner is respectfully reminded that the M.P.E.P. § 706.02(j) provides the following legal standard for establishing a *prima facie* case of obviousness:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

In response to our prior arguments presented in the Reply of March 22, 2006, the Examiner now cites to yet another secondary reference, the disclosure of Albert et al. The Examiner maintains the rejection as to only claims 11, 12, 19 and 20 and drops the prior rejection lodged against claims 1-6. The Examiner appears to be cobbling together a string of disclosures, almost as if using Applicants' own claims as a template based upon which the references are strung together in an invalid attempt to find disclosure of every element of the presently claimed invention.

Thus, the Examiner first cites to the disclosure of Leboulch et al. to find the disclosure of a vector comprising two loxP sites. Leboulch et al. is directed to methods of transforming cells through use of a retroviral vector, an acceptor vector and a donor vector. Arakai et al. is then relied upon as a secondary reference to modify Leboulch et al. to include lox71 and lox66. Arakai et al. is directed to integration using mutant lox sites in ES cells. The Examiner then cites

to an additional secondary reference, that of Albert et al., to provide motivation to again modify Leboulch et al. to include mutations in the lox sites found in the inverted repeat regions, not the spacer regions as disclosed in Leboulch et al. Thus, the Examiner is requiring one of ordinary skill in the art to so drastically modify the original disclosure of Leboulch et al. that it hardly resembles the original disclosure or its originally stated goals.

Additionally, Albert et al. is directed to use of vectors in plant cells, not mammalian cells. (See, Araki et al., page 868, column 2, second full paragraph, lines 4-7).

Thus, to so drastically modify the disclosure of any single reference, such as Leboulch et al., to substitute numerous elements chosen from the two secondary references, amounts to improper hindsight reconstruction. To establish the alleged case of *prima facie* obviousness, it is clear that the Examiner has dissected bits and pieces from each of the different references, each reference directed at solving different problems, and has combined these bits and pieces together in an attempt to create a combination and method similar to that defined by the claims of the present application. Through a process of impermissible hindsight reconstruction, the Examiner is improperly modifying and reconstructing the disclosures of the references to a point that they are taken entirely out of context to achieve the methods of the presently claimed invention. (See, *Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988), stating, "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit,'" (internal citation omitted); and *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988), stating

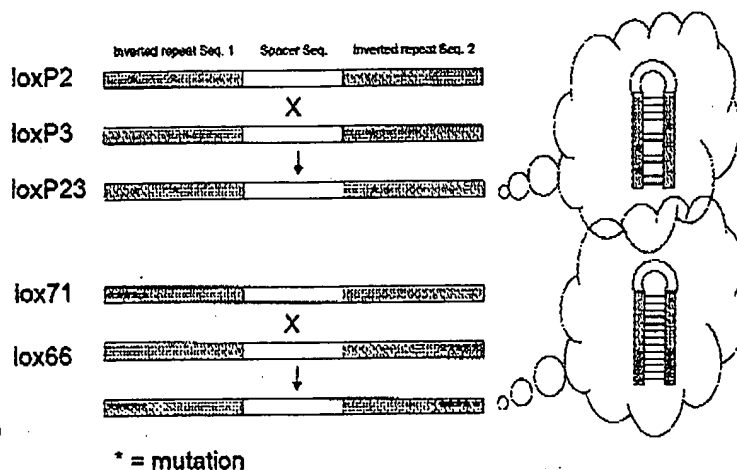
“One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.”).

Furthermore, claims 11, 12, 19 and 20 are directed to the acquisition of a trapped clone using a specific vector, and isolation of the trapped gene. None of the cited references disclose or suggest all the steps recited in claims 11 and 19, especially the last step, isolating the trapped gene.

Even further, that the disclosures are directed to different goals is highlighted as discussed below, by the difference in mechanisms of recombination. Thus, combination of the various elements of the references cited may actually yield inoperable embodiments because the mechanisms of recombination are different.

First, none of the cited references discloses a nucleotide comprising the nucleic acid sequence of SEQ ID NOS:15 and/or 16, as recited in claims 1 and 4, from which claims 11 and 12 depend. Thus, since the cited references do not disclose or suggest these specific nucleic acid sequences, the Examiner has failed to establish a *prima facie* case of obviousness for at least this reason with respect to claims 11 and 12.

Second, Albert et al. disclose the use of lox71 and lox66. However, although through combination of lox71/lox66, efficient recombination is expected, the chemical mechanism is different, as illustrated in the figure below:



The "lox72," generated from the combination of lox71/lox66 does not have any mismatches in the base pairs of the right and left inverted repeat sequences of the intermediate. Nonetheless, the recombination of lox72 is again inhibited.

Therefore, it would have been difficult to predict which combination may be replaced by any other combination in light of the disclosure of this reference because it discloses an entirely different mechanism of action. In fact, it is not certain whether any such combination would actually function. It is just as likely that the combination could be inoperable. One of ordinary skill cannot predict the possible outcome in this case since the mechanisms are so different.

Thus, since there exists no motivation in the cited references to combine the two disclosures in this way, and to suggest that such a combination might actually work as the presently claimed invention, the Examiner has failed to establish a *prima facie* case of obviousness.

Additionally, regarding claim 20, the Examiner has not provided a citation to any reference which either discloses or suggests the limitation of a trap vector which further comprises pA and PV, wherein pA is located downstream of the marker gene.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness with respect to claims 11, 12, 19 and 20 because 1) the disclosures of the cited references, either considered in combination or separately, do not disclose or suggest each and every element of the presently claimed invention, 2) the Examiner must resort to improper hindsight reconstruction to derive the presently claimed invention, and 3) the motivation to combine the references in such a way to derive the presently claimed invention cannot be found within the references themselves since they are directed at different goals and since the individual elements disclosed operate through different biochemical mechanisms. (See, *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)).

Reconsideration and withdrawal of the obviousness rejection of claims 11, 12, 19 and 20 are respectfully requested.

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CONCLUSION

If the Examiner has any questions or comments, please contact Thomas J. Siepmann, Ph.D., Registration No 57,374 at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Respectfully submitted,

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